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Review article

Protein-lipid nanohybrids as emerging platforms for drug and gene delivery: Challenges and outcomes

Mohamed Gaber[a], Waseem Medhat[a], Mark Hany[a], Nourhan Saher[a], Jia-You Fang[b,c,d,*], Ahmed Elzoghby[a,e,**]

[a] Cancer Nanotechnology Research Laboratory (CNRL), Faculty of Pharmacy, Alexandria University, Alexandria 21521, Egypt
[b] Pharmaceutics Laboratory, Graduate Institute of Natural Products, Chang Gung University, Taoyuan 333, Taiwan
[c] Research Center for Industry of Human Ecology and Research Center for Chinese Herbal Medicine, Chang Gung University of Science and Technology, Kweishan, Taoyuan 333, Taiwan
[d] Department of Anesthesiology, Chang Gung Memorial Hospital, Kweishan, Taoyuan 333, Taiwan
[e] Department of Industrial Pharmacy, Faculty of Pharmacy, Alexandria University, Alexandria 21521, Egypt

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A B S T R A C T

Nanoparticulate drug delivery systems have been long used to deliver a vast range of drugs and bioactives owing to their ability to demonstrate novel physical, chemical, and/or biological properties. An exponential growth has spurred in research and development of these nanocarriers which led to the evolution of a great number of diverse nanosystems including liposomes, nanoemulsions, solid lipid nanoparticles (SLNs), micelles, dendrimers, polymeric nanoparticles (NPs), metallic NPs, and carbon nanotubes. Among them, lipid-based nanocarriers have made the largest progress whether commercially or under development. Despite this progress, these lipid-based nanocarriers suffer from several limitations that led to the development of many protein-coated lipid nanocarriers. To less extent, protein-based nanocarriers suffer from limitations that led to the fabrication of some lipid bilayer enveloping protein nanocarriers. This review discusses in-depth some limitations associated with the lipid-based or protein-based nanocarriers and the fruitful outcomes brought by protein-lipid hybridization. Also discussed are the various hybridization techniques utilized to formulate these protein-lipid nanohybrids and the mechanisms involved in the drug loading process.

1. Introduction

Among the different types of clinically-used nano-formulations, lipid-based nanocarriers such as liposomes, lipid NPs, nanocapsules and nanoemulsions hold the biggest share. Many platforms exploit these lipid-based systems to deliver a variety of biologically active compounds due to the numerous benefits they confer such as being the least toxic for in-vivo applications [1–3]. These systems in general are biodegradable, biocompatible, non-immunogenic, and easy to prepare. They have been long used to alter drug properties and improve their therapeutic indices by modifying their absorption, reducing metabolism, decreasing toxicity, and increasing their biological half-lives. Liposomes can deliver both hydrophilic and hydrophobic drugs in their aqueous cores and hydrophobic bilayer coronas, respectively. Similarly, SLNs can incorporate both hydrophilic and hydrophobic drugs by means of high pressure homogenization (HPH) technique. Also, these systems have been a better alternative for gene delivery purposes instead of viral vectors due to their non-antigenicity and ability to protect DNA from inactivation [4–6].

Despite the abovementioned advantages, all lipid-based nanocarriers seem to suffer from several disadvantages that hinder their promising progress. First, their colloidal and biological instabilities caused by their in vivo interactions with serum proteins and non-specific binding to cells such as lymphocytes, erythrocytes and endothelial cells. Second, in vivo, all lipid-based nanocarriers seem to suffer from increased reticuloendothelial system (RES) clearance [7–9]. This is caused by opsonization of lipid nanocarriers by complement proteins, fibronectin, and immunoglobulins which occurs mainly due to their hydrophobicity, rigidity, and/or their surface charges. As a result, this shortens their blood circulation times, and hence diminishes their efficacy. In addition, lipid nanoemulsions also suffer from rapid drug release due to the liquid state of their lipids. This in particular is not the case with SLNs which can offer a more sustained drug release due to their lipids' solid state. However, HPH commonly used to formulate

* Corresponding author at: Pharmaceutics Laboratory, Graduate Institute of Natural Products, Chang Gung University, Taoyuan 333, Taiwan.
** Corresponding author at: Cancer Nanotechnology Research Laboratory (CNRL), Faculty of Pharmacy, Alexandria University, Alexandria 21521, Egypt.
E-mail addresses: fajy@mail.cgu.edu.tw (J.-Y. Fang), ahmed_elzoghby@alexu.edu.eg (A. Elzoghby).

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SLNs may affect the stability of shear-sensitive drugs [10–12].

Numerous approaches were developed with the purpose of extending the circulation times of lipid carriers. PEGylation has been the most widely applied approach to reduce RES clearance due to the hydrophilicity, molecular flexibility, and neutrality of PEG. PEGylation decreases opsonization by providing a hydrated molecular corona around the nanocarrier, shielding surface charges, and becoming a steric barrier for opsonins to bind which extends blood circulation times of these PEGylated nanocarriers. However, PEG is not efficiently degraded by human enzymes leading to its accumulation in vivo, and hence subsequent toxicities could occur. Also, the reproducibility of PEGylated nanocarriers is relatively low and reports on its immunogenicity are not infrequent. As a result, a number of alternative approaches were developed. Coating the lipid nanocarriers with biodegradable proteins such as albumin, gelatin, silk fibroin (SF), and transferrin (Tf) that can carry the same functions as PEG seemed reasonable [13–15]. On one hand, these proteins can provide a hydrophilic corona, shield surface charges, and sterically hinder opsonin-binding in the same fashion as PEG, but on the other, their biodegradability and non-antigenicity have been well established. Also, these proteins can carry a lot of other different functions that PEG could not carry. For instance, some proteins can actively target particular tissues such as tumor cells by means of interaction with specific receptors overexpressed on these cells [16–19]. Moreover, the numerous functional groups available in protein structure can facilitate conjugation of drug or targeting ligand. In addition, proteins can enhance cellular uptake or gene transfection efficiency, enhance brain or ocular delivery of lipid-based nanocarriers, all of which PEG could not carry [20–24]. Through this review, we explain the limitations of lipid-based nanocarriers and the outcomes brought by their hybridization with different naturally-occurring proteins. In addition, we discuss the approaches that studied the consequences of encapsulation of protein nanocarriers within lipid bilayer coating. The various hybridization techniques and drug loading mechanisms utilized in the formulation of these protein-lipid nanohybrids are also discussed.

2. Hybridization techniques

In many studies, the surface of lipid nanocarriers including liposomes, SLNs, lipoplexes and lipid nanoemulsions was successfully functionalized with proteins via different mechanisms including covalent conjugation, desolvation, HPH, emulsification, or electrostatic coating. In few studies, protein nanocarriers were encapsulated within liposomes via film hydration, modified desolvation, and solvent injection methods.

2.1. Chemical conjugation

Several methods have been approached with the purpose of forming covalent bonds between proteins and lipid nanocarriers, however, the carbodiimide coupling method has been the most commonly applied one. This could be ascribed to it being a zero-length crosslinker, thus avoiding detrimental effects of intervening linkers or antibody formation against them. Also, of the two basic carbodiimide subtypes, the water soluble carbodiimide (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, EDC) is the most frequently utilized due to the hydrophilicity of most proteins and the hydrophilicity of its reaction by-products allowing easy purification. Carbodiimides are usually used in facilitating amide bond formation between carboxylic and amine groups which are both widely available on lipids and proteins. Furumoto et al. used *N*-glutarylphosphatidyl ethanolamine (NGPE) in the formulation of liposomes to provide a carboxylic functionality that could be exploited in amide bond formation with the amino groups of albumin. First, NGPE carboxylate was activated using EDC and the reactive intermediate formed was stabilized with *N*-hydroxysuccinimide (NHS). Then, the unreacted EDC was quenched with 2-mercaptoethanol to avoid activation of the carboxylic groups on albumin upon its addition thus avoiding self-polymerization [25]. Similarly, the carbodiimide method has been employed in forming gelatin-oleic acid (OA) conjugates [26], Tf-coated liposomes [27], and Tf-coated SLNs [28].

Activation of carboxylic functionalities of lipid components followed by conjugation to amino groups of the protein was found to yield lower sizes and higher conjugation efficiencies than the activation of protein carboxylic groups. The reason behind this is that proteins can self-polymerize upon activation owing to the existence of both, carboxylic and amino functionalities. In a study by Pooja et al., two different carbodiimide strategies were compared in the achievement wheat germ agglutinin (WGA)-coated paclitaxel (PTX)-loaded SLNs. In the first one, stearyl amine was used to form SLNs to provide an amino group that could be coupled to the activated carboxylic group of WGA. Upon coupling, size increased from 149.8 nm to 239.2 nm and the conjugation efficiency was low, being just 11.45%. In the second strategy, stearic acid was used in the formation of SLNs to provide a carboxylic group that could be coupled to amino groups of WGA. Size increased to just 197.4 nm while the conjugation efficiency was significantly higher, being 74.1% [29].

On another avenue, the carbodiimide coupling method was not applicable for hybridization when the pH-remote loading method was utilized for encapsulation of doxorubicin (DOX) into liposomes. For efficient hybridization, the carbodiimide reaction has to be conducted under weakly acidic conditions thus making the efficient pH-remote loading of DOX unavailable. Alternatively, Yokoe et al. hybridized albumin with PEGylated liposomes containing dioleoylphosphatidyl ethanolamine (DOPE) via a hetero-bifunctional crosslinker, *N*-succinimidyl 3-(2-pyridyldithio)propionate (SPDP). The NHS ester end of SPDP forms an amide bond with amine-containing molecules while the pyridothiol group at the other end can form a disulfide bond with sulfhydryl residues. These sulfhydryl residues could be created on proteins with SPDP itself by reducing it with disulfide-reducing agents such as dithiothreitol (DTT) (Fig. 1a). First, an amide bond was formed between SPDP and DOPE to create a sulfhydryl-reactive DOPE. Then, sulfhydryl functionalities were created on albumin by coupling it first with SPDP then reducing it with DTT. Finally, a disulfide bond was formed upon the addition of albumin onto liposomes containing the sulfhydryl reactive-DOPE (Fig. 1b) [30].

Thiol-maleimide coupling technique has been widely exploited to form thioether linkages between maleimide-derivatized lipids and thiolated proteins. Thöle et al. prepared thiolated albumin using the hetero-bifunctional crosslinker, *N*-succinimidyl-*S*-acetyl-thioacetate (SATA). Then, PEGylated liposomes containing thiol-reactive maleimide were incubated with thiolated albumin leading to the formation of a thioether bond between maleimide and thiol functionalities [31]. In a similar way, Tf was thiolated using Traut's reagent and then it was added to maleimidobenzoyl-DOPE leading to the formation of Tf-conjugated lipids that were further used as a coating for PLGA NPs [32]. However, the thiol-maleimide coupling is faced with limited specificity for thiols and limited hydrolytic stability which led Xu et al. to exploit Staudinger ligation in conjugating Tf to DOPE. In Staudinger ligation, an azide-containing molecule reacts with a triphosphine derivative to form an aza-ylide intermediate. The triphosphine derivative contains an electrophilic trap, a methyl ester, which attacks the nucleophilic nitrogen of the intermediate. The result of such rearrangement is an amide bond between the azide-containing molecule and the triphosphine-containing molecule. DOPE was first activated with 2-(diphenylphosphino)terephthalic acid 1-methyl 4-penta-fluorophenyl-diester (DPPTPA) which provides a triphosphine for azide reaction and a methyl ester for the subsequent electrophilic trapping. Then, Tf was activated with p-azidophenyl isothiocyanate to react with liposomes containing the activated DOPE to form Tf-functionalized liposomes [33].

Using monoethanolamine (MEA) as a water soluble activator, an amphiphilic conjugate was fabricated from gelatin and OA by an

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